REMARKS

Applicants thank Examiner S. Kaushal and Supervisory Patent Examiner Joseph Woitach for kindly holding a most helpful personal interview with applicant and applicants' representative on June 24, 2008. Applicants are in agreement with the substance of the interview summary prepared the same day. This Reply reflects the discussion in the interview.

Election/ Restriction Requirement and claims currently under consideration

Applicants have elected Group II (induction of cardiomyogenesis) to be searched and examined; claims to the methods of Groups I, III and IV are canceled.

With regard to the species election, applicants request that claims which recite non-elected species be examined if the elected species are found to be free of the prior art of record.

Amendments to the claims

Some of the claims have been amended to address points raised by the Examiner and/or to clarify aspects of the invention. The amendments are fully supported by the specification and do not add new matter.

The claims have been amended to be directed solely to *in vivo* administration of a plasmid, to a subject. Claims directed to *in vitro* or *ex vivo* administration are canceled without prejudice or disclaimer. Applicants reserve the right to pursue these embodiments of the invention in a continuation application.

Some of the claims (*e.g.* claims 1 and 65) have been amended to recite the dosage of the polynucleotide being administered. This amendment is supported, *e.g.*, by claims 98 and 99.

Some of the claims (*e.g.* claims 1 and 65) have been amended to delete the recitation of arteriogenesis, lymphangiogenesis or vasculogenesis, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of the canceled embodiments of the invention in a continuation application.

Some of the claims (*e.g.* claims 1 and 65) have been amended to delete the recitation of an active site of the VEGF; and dependent claims directed to these embodiments of the invention (*e.g.*

claims 26 and 27) have been canceled, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of these embodiments of the invention in a continuation application.

Some of the claims (*e.g.* claims 1 and 65) have been amended to clarify that the plasmid is administered directly to a cardiomyocyte or a tissue comprising cardiomyocytes. For example, the method of delivery of the plasmid may be intramyocardial muscle administration (*e.g.*, claim 43), which can be, *e.g.*, transepicardial administration or transendocardial administration (*e.g.*, claim 44). Claims directed to other means of administration (*e.g.* claims 37-42 and 45-47 have been canceled, without prejudice or disclaimer. Applicants reserve the right to pursue prosecution of these embodiments of the invention in a continuation application.

Other claims have been amended to correct claim dependency or to eliminate duplicative claims, to be consistent with the claims as currently amended.

The amendment to claim 34 is supported, *e.g.*, at page 6, lines 3-5 of the specification.

In addition to the claims which have been previously canceled, claims 3-10, 26-27, 33, 37-42, 45-50, 57-58, 71, 74-75, 100-101 and 104 have been canceled. Thus, claims 3-10, 15-18, 26-30, 32-33, 37-42, 45-50, 57-58, 63, 67-68, 70-71, 74-75, 81-97, 100-101 and 104 have been canceled.

New claim 105 is fully supported by the specification. For example, Example V shows that administration of a dose of the plasmid that is effective to induce cardiomyogenesis also results in the induction of arteriogenesis. If claims directed to the induction of cardiomyogenesis are patentable, then dependent claims which recite further limitations should also be patentable.

Claims 1, 2, 11-14, 19-25, 31, 34-36, 43-44, 51-56, 59-62, 64-66, 69, 72-73, 76-80, 98-99, 102-103 and 105 are currently under consideration.

Claim objection

Amended claim 1, which was objected to as being directed to a non-elected invention, now recites a method for inducing cardiomyogenesis, which is the elected embodiment of the invention.

Enablement rejections

The Examiner alleges that "active sites" of VEGF 1-165 are not adequately enabled by the specification. Applicants disagree, for reasons of record. Nevertheless, in an effort to expedite prosecution, claims 1 and 65 have been amended to delete the recitation of "active site."

The Examiner alleges that the claimed methods of delivery do not allow for selective targeting of cells *in vivo*, and thus are not adequately enabled for this purpose by the specification. Applicants disagree, for reasons of record. Nevertheless, in an effort to expedite prosecution, the claims (*e.g.*, claims 1 and 65) have been amended to clarify that the method of delivery is direct administration to a cardiomyocyte or a tissue comprising cardiomyocytes, *e.g.* intramyocardial administration (direct administration to the myocardium), as recited in claim 43, and that this can be accomplished by, *e.g.*, (1) transepicardial administration (injection into the heart muscle during surgery) or by (2) transendocardial administration (using a catheter to introduce the plasmid into heart muscle), *e.g.* as recited in claim 44. In any of these methods, the plasmid is introduced directly into the target cardiomyocyte cell or tissue comprising cardiomyocytes, thereby obviating the delivery problems alleged by the Examiner to be problematic.

The Examiner alleges that applicants' referral to the Vera Janavel publication of 2006 (Vera Janavel *et al.* (2006) *Gene Therapy* 13, 1133-42) does not contribute to the enablement of the claims, because the paper was published after the filing date of the application. This allegation is unjustified. In the first place, the data presented in the application as filed, using the pig model, show that a gene therapy method of the present claims results in at least arteriogenesis and cardiomyogenesis. This disclosure alone is sufficient to enable the claims. Furthermore, and supplementally, in Example VI, starting on the bottom of page 35 of the U.S. C.I.P., the application states that "Plasmids as above have also been introduced into sheep suffering form acute myocardial infarction, and myocardiogenesis has been observed. The methods in this study were adapted from methods used in the preceding Examples." The Vera Janavel (2006) paper was provided to the Examiner merely to supplement and enlarge upon the (already enabling) statement made in the patent application. Thus, the paper should not be dismissed as being merely "post-filing" information.

With regard to the allegation that the application does not disclose the induction of "mitosis or proliferation of cardiomyocytes," applicants respectfully point out that the induction of cardiomyogenesis, which is demonstrated in the application is, in fact, the mitosis or proliferation of cardiomyoctes. See, *e.g.*, the summary of methods used to assay for mitosis, *e.g.*, at pages 30-31 of the specification; and the results showing that mitosis and cell division of cardiomyocytes do, in fact, occur, *e.g.*, at pages 32-33 and the figures and table referred to therein. See also the discussion of "cardiomyogenesis" in Appendix A.

With regard to the claimed treatments of ischemic heart disease, myocardial infarction (*e.g.* acute myocardial infarction), myocardial ischemia (*e.g.*, chronic myocardial ischemia), dilated cardiomyopathy and heart failure, the demonstration in the present application of the induction of cardiomyogenesis and arteriogenesis clearly indicates that the preceding conditions can be treated by a method of the invention. These conditions exhibit shared pathophysiological features, *e.g.* myocardial cell loss (which can be treated by inducing cardiomyogenesis) and hypoperfusion (which can be treated by inducing arteriogenesis).

More particularly, the inventors have demonstrated that cardiomyogenesis occurs following treatment by a method of the invention of acute myocardial infarction in sheep. See, *e.g.*, Example VI of the application and the supplemental data shown in Vera Janavel *et al.* (2006), *Gene Ther.* 13, 1133-42, a paper by the inventors and their collaborators, which was provided to the Examiner in the Reply filed June 29, 2007 and which is submitted in an IDS that is filed concurrently with the present Reply. At least two forms of heart disease are direct sequelae of acute myocardial infarction: heart failure (*e.g.*, infarction-related heart failure) and dilated cardiomyopathy. The inventors, at least one of whom is a physician who specializes in cardiology, have informed us that a physician encountering either of these conditions would know that the most probable cause was acute myocardial infarction, and would recognize the benefit of treating such a patient with a method that stimulates cardiomyogenesis. The enablement of treatment of these three conditions (species), alone, would enable the treatment of the genus of *in vivo* treatments recited in claim 1.

Furthermore, the specification demonstrates that cardiomyogenesis occurs following treatment by a method of the invention of pigs having chronic myocardial ischemia, which is an animal model not only for myocardial ischemia (including chronic myocardial ischemia), but also

for ischemic heart disease. Some of the cardiomyogenesis shown in these pig experiments was probably occurring in the ischemic cells. However, even if cardiomyogenesis had not occurred in the ischemic tissue, itself, the inventors have informed us that cardiomyogenesis in other regions of the heart would benefit subjects suffering from at least the ischemic conditions noted above, including ischemia-related heart failure. Therefore, the specification enables methods directed to treating at least any of the five heart conditions noted (and underlined) above and recited in claim 34.

The Examiner has failed to meet his burden to provide evidence or sound scientific reasoning showing that the indicated disease conditions can not be treated by a method of the invention.

In view of this large number of species of heart conditions that are enabled, it is believed that the genus of *in vivo* treatment recited in claim 1 ("A method for inducing cardiomyogenesis in a subject in need of such treatment") is also enabled by the specification.

Rejections under 35 USC 112, second paragraph

Claim 1, from which claims 2, 57 and 66 depend, has been amended to correct the typographical error, thereby obviating the rejection of claims 2, 57 and 66 as allegedly lacking antecedent basis.

Rejections (anticipation or obviousness) over Vale *et al.* (2000) *Circulation* 102, 965-974 ("Vale *et al.*")

Contrary to the allegation of the Office Action, Vale *et al.* neither anticipates nor renders obvious the instant claims.

Recognizing that the terminology related to cardiology and methods of studying heart function is rather specialized, applicants provide some non-limiting background information explaining some of the terms and methods found in Vale *et al.* and in the present application, and how they relate to the instant claims. This background information is presented as Appendix A. The literature materials from which this discussion was taken will be provided to the Examiner upon request.

This background information should aid the Examiner in recognizing that Vale *et al.*'s report that the administration of low levels of a VEGF plasmid can augment perfusion of ischemic myocardial tissue and can restore some function (as measured by LLS by the NOGA method) to the ischemic tissue is entirely different from the method of the present claims, in which the administration of an effective amount of VEGF plasmid (a significantly higher amount than that disclosed by Vale *et al.*) can actually induce cardiomyogenesis (the mitosis or proliferation of cells which can, *e.g.*, lead to the replacement of dead cells in an infarcted area). The LLS measurement in the Vale *et al.* reference merely reflects the health of the cells; it does not reflect the number of cells. These points were presented in detail in the Reply filed June 29, 2007 and will not be repeated in the present Reply. Note in particular the discussion on page 16, second full paragraph of that Reply, which points to evidence in the application as filed that the claimed method does bring about cardiomyogenesis.

The reference does not anticipate the present claims, at least because the reference does not teach the dose of polynucleotide that is recited in, *e.g.*, claim 1. (Although applicants disagree with the allegation by the Examiner during the personal interview of June 24, 2008 that the term "a dose being sufficient to induce cardiomyogenesis" fails to distinguish the claim from the Vale *et al.* reference, applicants have, at the suggestion of the Examiner, inserted the dosage into claim 1.) The amount of plasmid polynucleotide recited in these claims is significantly higher that the amount of plasmid reported in the reference. Vale *et al.*'s method to augment perfusion and restore some function to ischemic tissue would not, inherently, result in the much more difficult task of stimulating cardiomyogenesis. In the Declaration under 37 CFR 1.132 that is attached hereto as Appendix B, Dr. Roger Laham, a respected expert in the field of cardiology and heart angiogenesis, declares that neither he nor a worker of ordinary skill, upon reading the Vale *et al.* reference, would have recognized that its method would necessarily have stimulated cardiomyogenesis. See, *e.g.*, paragraphs 8 and 10 of the Declaration. In order to inherently anticipate a claimed effect, a reference must necessarily and inevitably give rise to that effect. That is not the case here.

Furthermore, the reference does not render the present claims obvious, at least because there would have been no expectation that Vale *et al.*'s method, which augments perfusion and restores some function to ischemic tissue, would also result in cardiomyogenesis. There would have been no

motivation, with a reasonable expectation of success, to try using higher amounts of plasmid, in order to stimulate cardiomyogenesis. The stimulation of cardiomyogenesis is considerably different from merely "improving" the restoration of function to ischemic tissue by augmenting perfusion of the tissue. In support of this argument, Dr. Laham, in the attached Declaration under 37 CFR 1.132, declares that, in his opinion, the Vale *et al.* reference does not suggest or disclose that the dose of VEGF1-165 administered in the reference is effective to induce cardiomyogenesis. See, *e.g.*, paragraphs 6 and 10 of the Declaration.

In fact, it was not until after the present inventors had reported [Laguens *et al.* (December, 2002) *Gene Therapy* 9, 1676-81] that cardiomyogenesis occurs following the administration of a sufficient amount of polynucleotide encoding the growth factor, VEGF, that others in the field recognized that this unexpected phenomenon can occur. Subsequently, a number of papers were published by other researchers, confirming that the administration of polynucleotides encoding additional growth factors, *e.g.*, LIF, FGF5, Cyclin A2 and FGF1/p38, as well as VEGF 1-165, resulted in cardiomyogenesis. See, *e.g.*, Zou *et al.* (2003) *Circulation* 108, 748-753; Suzuki *et al.* (2005) *Circulation Research* 96, 767-775; Woo *et al.* (2006) *Circulation* 114, I-206-I213; Engel *et al.* (2006) *PNAS* 103, 15,546-551; and Guerrero *et al.* (2008) *J. Interv Cardiol* 21, 242-251, respectively. Some of these papers referenced the findings of the present inventors. These papers will be provided to the Examiner upon request.

Furthermore, Dr. Laham attests in the attached Declaration under 37 CFR 1.132 that it would have been unexpected at the time of filing of the application that one would be able to induce cardiomyogenesis by *any* method of gene therapy, let alone by introducing nucleic acid encoding VEGF, a protein which, until the time of the invention, was only thought to act as a growth factor for endothelial cells (not for cardiomyocytes). See, *e.g.,* paragraph 9 of the Declaration.

In further support of the non-obviousness of the present claims, it is noted that the ability to stimulate cardiomyogenesis provides advantages over the method of Vale *et al.*, in that the presently claimed method allows for the treatment of conditions that benefit from the replacement of non-viable or even lost (dead) cells, such as myocardial infarction or heart failure. See, *e.g.*, paragraph 11 of the Declaration. These advantages were not evident from the cited reference, further supporting the non-obviousness of the present claims.

With regard to the allegation by the Examiner that the introduction of high levels of plasmid was merely routine optimization, applicants note that after the Vale *et al.* paper was published in 2000, a clinical trial in which polynucleotides encoding VEGF were administered to human patients used the highest dose reported by Vale *et al.* (0.5 mg/ human subject). And this trial proved to be unsuccessful. It was not until the present inventors had published their findings in December, 2002 that somewhat higher doses were used in a second clinical trial (2.0 mg/ human subject). This trial, too, reported negative results.

More specifically, in the first of these carefully controlled clinical trials, the EuroInject One Phase II trial, patients suffering from severe coronary artery disease were administered a total dose of 0.5 mg of a plasmid encoding VEGF 1-165, via intramyocardial injection. This study was reported in Kastrup *et al.* (2005) *J. of the American College of Cardiology* 45, 982-988, a copy of which is submitted in the IDS filed concurrently with this Reply. The dosage is given on page 983, in the section entitled "Intramyocardial injections." Clearly, these investigators were not motivated to use a higher dose than that disclosed in the Vale *et al.* paper. The paper reports that "no significant treatment effect was observed at stress-induced perfusion defects." See, *e.g.*, the Conclusion on page 988.

In the second of these carefully controlled clinical trials, the Northern trial, which was apparently initiated after the EuroInject One trial was published, patients having refractory angina were administered 2.0 mg of a plasmid encoding VEGF 1-165, via intramyocardial administration. A copy of the report of the Northern trial is submitted in the IDS filed concurrently with this Reply. [Due to a scanning error in this report, the amount of plasmid administered appears as "2000□g" instead of "2000μg." Confirmation that the amount used was actually 2000μg is shown on page 381, 2nd paragraph, of a later review article mentioning this study: Lekas *et al.* (2006) *Curr Opin Cardiol* 21, 376-84, which is also submitted in the IDS which is filed concurrently with this Reply.] The use of a higher dose of plasmid may have been influenced by the suggestion by the present inventors, in their December 2002 publication, to use higher doses. The results of this study, as reported on October 23, 2007 at an annual international conference held in Washington, DC, entitled the "TCT: Transcatheter Cardiovascular Therapeutics, Cardiovascular Research Foundation," indicated that "There was no improvement in myocardial perfusion, exercise tolerance, or symptom class at 3 or 6

months in patients receiving plasmid DNA compared with saline (placebo). The lack of benefit of VEGF gene transfer was observed even in patients with more limited coronary disease (group 2). ... This study provides compelling evidence of lack of benefit of [the trial] for the treatment of patients with chronic refractory angina." An Abstract of this report is submitted in the IDS filed concurrently with this Reply.

Not only did these two clinical trials fail to use a significantly higher dose than was disclosed by Vale *et al.*, which attests to the lack of motivation in the field to use significantly higher doses in order to improve upon the earlier results, but both of the clinical trials were unsuccessful, even in inducing therapeutic amounts of angiogenesis. These failures provide strong, objective evidence to support the argument presented in the present Reply that the higher doses which are presently claimed provide surprising, unexpected, results.

As noted above, to further support the arguments against non-obviousness, attached as Appendix B is a Declaration under CFR 1.132 by an recognized expert in the field of cardiology and heart angiogenesis, Dr. Roger Laham, of Harvard University. In the Declaration, Dr. Laham emphasizes that the augmentation of perfusion and partial restoration of myocardial function in the affected ischemic tissue reported by Vale *et al.* following the administration of relatively low levels of VEGF plasmid is qualitatively different from the demonstration by the present inventors that administration of relatively large levels of VEGF plasmid can actually induce cardiomyogenesis (mitosis and cell proliferation). The induction of cardiomyogenesis provides an advantage in that it allows for the treatment of conditions, such as heart failure, myocardial infarction, and others, which cannot be affected by the mere restoration of cardiac activity in ischemic tissue by increased perfusion. Dr Laham declares that he, and other experts in the field at the time the invention was made, would have found the findings of the present inventors to be surprising and unexpected.

In response to other allegations in the Office Action mailed October 5, 2007 and in the Advisory Action of April 18, 2008, applicants have the following comments:

Contrary to the allegation by the Examiner, it is not necessary to specifically recite in the broad claims that, *e.g.*, the mitotic index is increased. The increase in mitotic index is, by definition, a property associated with "cardiomyogenesis."

The term "VEGF 1-165" does not constitute new matter. See, *e.g.*, the specification at page 7, last line.

Contrary to the assertion by the Examiner, Vale *et al.*'s observation that the size of the ischemic area was decreased does *not* indicate that cardiomyogenesis took place; rather, it merely shows that some cardiac function was restored to the ischemic tissue being studied, presumably by virtue of the stimulation of perfusion in the affected area. As was emphasized above, the LLS measurement in the Vale *et al.* reference merely reflects the health of the cells; it does not reflect the number of cells. This distinction is elaborated upon in Appendix A, which provides definitions and explanations of terms and methods in Vale *et al.* and in the present application.

In the Office Action of October 5, 2007, the Examiner cites **Kajstura *et al.*** as allegedly showing that ischemic myocardium is inherently associated with cardiomyogenesis. For a variety of reasons, which will be elaborated upon in depth if the Examiner requests, the Kajstura *et al.* reference is not relevant to the present invention. For example, the measurement methods used in the reference would have been expected to give rise to an artifactual overestimation of the number of mitotic cells. Later, when other investigators employed more appropriate measurement methods, they were unable to reproduce the report by Kajstura *et al.* of naturally occurring cardiomyogenesis in, *e.g.*, ischemic or infarcted tissue. Moreover, the patients studied in the Kajstura *et al.* reference were in end-stage ischemic heart disease; in fact, the patients had died from the disease before their tissues were studied. The Kajstura reference reflected a different scenario from the subjects in the present study, who suffered from chronic ischemic heart disease that was not end-stage disease, and which constituted a more suitable class of subjects for demonstrating the effectiveness of a method of the invention.

The appropriate comparison to establish that a method of the invention results in cardiomyogenesis in a subject (*e.g.* having chronic ischemia) is to compare the amount of cardiomyogenesis in subjects treated with a plasmid encoding the VEGF, to the amount of cardiomyogenesis in a placebo group of subjects treated with a plasmid lacking the VEGF coding sequences. As is shown in Table 6 of the specification, treated subjects ("Group I-T") exhibited a greater than five times higher mitotic index than the placebo controls ("Group I-P").

In view of the preceding arguments and amendments, it is believed that the application is in condition for allowance, which action is respectfully requested. The Examiner is invited to contact applicants' representative by telephone before issuing an Office Action, if he feels a teleconference would be helpful to expedite allowance of the claims.

The Commissioner is hereby authorized to charge any fees association with this response or credit any overpayment to Deposit Account No. 22-0261, citing Docket No. 42597-193226.

Respectfully submitted,

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Appendix A

Myocardial ischemia is a condition in which oxygen deprivation to the heart muscle is accompanied by inadequate removal of metabolites because of reduced blood flow or perfusion. During ischemia, an imbalance occurs between myocardial oxygen supply and demand. Ischemia may manifest as (1) anginal discomfort *("angor pectoris")*, (2) EKG changes, (3) reduced uptake in myocardial perfusion images, or (4) regional or global impairment of ventricular function.

By contrast, **myocardial infarction** (MI) is the *irreversible* necrosis of heart muscle secondary to prolonged ischemia. In other words, if the cause of ischemia persists for a period of time (hours) then heart muscle death occurs. MI leads to impairment of systolic function or diastolic function and to increased predisposition to arrhythmias and other long-term complications. **Necrosis**, in turn, is the pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage; earliest irreversible changes are mitochondrial, consisting of swelling and granular calcium deposits seen by electron microscopy; most frequent visible alterations are nuclear: pyknosis, shrunken and abnormally dark basophilic staining; karyolysis, swollen and abnormally pale basophilic staining; or karyorrhexis, rupture and fragmentation of the nucleus. After such changes, the outlines of individual cells are indistinct, and affected cells may become merged, sometimes forming a focus of coarsely granular, amorphous, or hyaline material.

Diamond *et al.* (1978) *Am Heart J* 95, 204-9 suggested that ischemic non-infarcted myocardium can exist in a state of functional **hibernation**. Rahimtoola (1989) *Am Heart J* 117, 211-221 proposed the concept of **hibernating myocardium**, as a "chronic *reversible* left ventricular dysfunction due to coronary artery disease".

Following the recognition of the clinical implications of hibernating myocardium, a new concept arose in cardiology, **myocardial viability**, which refers to any myocardial tissue that is *not* infarcted, including myocardial ischemia and hibernating myocardium. In patients with left ventricular dysfunction, revascularization is the treatment of choice only if myocardial viability is

present. That is, improvement of left ventricular dysfunction can only be achieved when myocardial viability is present. Patients with viable myocardium may improve in function after revascularization, whereas patients without viable myocardium do not improve in function. Various non-invasive imaging techniques for assessing viable myocardium and the consequent prediction of improvement in left ventricular function after revascularization have been reported; *e.g.* single photon emission computed tomography (SPECT), as employed in the Vale *et al.* reference. If the presence of ischemia, as well as hibernating myocardium, can be demonstrated, the likelihood of functional recovery after revascularization increases.

Revascularization is a therapeutic method by which physicians enhance myocardial blood flow to the myocardium. It can be achieved by different medical procedures, such as PTCA (percutaneous transluminal coronary angioplasty) and CABG (coronary artery bypass grafting). The augmentation of perfusion, *e.g.* by angiogenesis, is another way to revascularize the myocardium.

Therapeutic revascularization (*e.g.* therapeutic angiogenesis) - in this case, stimulation of the induction of new blood vessels in viable myocardium - would be expected to improve left ventricular function. However, when perfusion (*e.g.*, angiogenesis) is stimulated in non-viable (dead = necrotic = infarcted) myocardium, no improvement of left ventricular function would be expected. Therefore, the revascularization method of Vale *et al.* would not be expected to lead to improvement of left ventricular function. By contrast, therapeutic cardiomyogenesis - the replication of cardiomyocytes - would be expected to improve left ventricular function, not only in viable, but also in non-viable myocardium.

Cardiomyogenesis refers to the replication (mitosis and proliferation) of cardiomyocytes (cardiac muscle cells), which leads to the regeneration of heart tissue. This physiological process can be used as a therapeutic method to regenerate diseased myocardium.

The **NOGA method** employed in Vale *et al.* can distinguish between ischemic and dead (infarcted) tissue; the Vale *et al* paper clearly shows that the tissue they examined was ischemic, but not dead.

The NOGA method is able to assess 2 major parameters to distinguish between normal, ischemic and infarcted tissue: myocardium voltage and function. The patterns are as follows:

- Normal myocardium: normal voltage and function
- Hibernating myocardium: normal voltage and impaired function
- Infarcted myocardium: impaired voltage and function

One of the NOGA results for voltage is called "unipolar endocardial potentials" (UpV). The NOGA result for function is called "linear local shortening" (LLS). For a further discussion of these terms, see, *e.g*, Vale *et al.* at page 966, under the title "LV (NOGA) Mapping" and references 13, 14 and 16 referred to therein.

The three patterns are summarized in the following chart:

	Normal myocardium	Ischemic Myocardium (Hibernating)	Dead Myocardium (Infarcted)
Unipolar endocardial potentials (UpV)	≥5 mV	≥5 mV	< 5 mV
Linear Local Shortening (LLS)	≥12%	4% to 12%	< 4%

In particular, Vale *et al.* states that "Local functional analysis (wall motion) is based on linear local shortening (LLS), a parameter that calculates the fractional shortening of regional endocardial surfaces at end systole. Unipolar (UpV) and bipolar (BpV) endocardial potentials are recorded from the tip electrode, and measurements that are based on these local intracardiac signal amplitudes formulate a guide to myocardial viability. The combination of these 2 data sets permits assessment of electromechanical function that identifies foci of myocardial ischemia. For example, for a given region of interest, UpV ≥5 mV (suggesting viable myocardium) and normal (≥12%) LLS (suggesting normal contraction) would indicate normal myocardium. In contrast, UpV < 5 mV and abnormal (< 4%) LLS (signifying severe regional hypokinesis or akinesis) would indicate a site of LV infarction. Alternatively, UpV ≥5 mV and abnormal LLS of 4% to 12% (indicating mild to

moderate impairment of contractility) would suggest a site of ischemic hibernating myocardium.(13,16)." (p. 966, bottom of column 1, beginning of column 2).

Also, see "Mean UpV and BpV recordings ≥5 mV and ≥2 mV, respectively, defining myocardial viability in the ischemic zone, did not change significantly after **GTx** (Table 2) " (p. 967, col 2, paragraph 2).

The data presented by Vale *et al.* indicate that the tissue being examined was viable myocardium, in particular chronic myocardial ischemia with hibernating myocardium.